The Pharmacotherapy of Social Anxiety Disorder

a report by
Mark H Pollack, MD

Director, Center for Anxiety and Traumatic Stress Disorders, Massachusetts General Hospital, and Professor of Psychiatry, Harvard Medical School

Though once dubbed a “neglected anxiety disorder,” social anxiety disorder (SAD; also known as social phobia) has been the focus of increasing research and clinical attention over the last 10–15 years as its high prevalence and attendant morbidity has been well documented. The initial emphasis on the use of monoamine oxidase inhibitors (MAOIs) for this condition—with their attendant daunting list of potential adverse effects—may also have contributed to the relatively low rate of recognition and treatment in clinical practice. With the demonstration of the clear efficacy of better tolerated and safer pharmacotherapies, as well as the availability of specific cognitive–behavioral therapy (CBT) programs, the barriers to treatment of SAD have gradually been reduced, although the disorder remains underdiagnosed and undertreated. Although this brief article will focus on pharmacological approaches to the treatment of SAD, it should be noted that a psychosocial intervention (CBT) has demonstrated comparable efficacy to standard pharmacotherapy for the treatment of SAD; however, based on the available evidence it is likely that other agents from these classes are effective as well, although differences in side effect profiles may be clinically relevant in some cases. Initiation of significant therapeutic effects usually takes at least two to three weeks, with benefits accruing over weeks or months as patients begin to expose themselves to previously feared situations.

**Beta-blockers**

Though not effective as primary treatments for generalized SAD, beta-blockers—including propranolol and atenolol—are useful for the treatment of ‘performance anxiety’ about public speaking or other performance situations. By blunting symptoms of physiological arousal such as tachycardia and tremor, which are often an individual’s focus in social situations, the beta-blockers appear to interrupt the escalating fear cycle that drives further anxiety during performance. Pindolol, a beta-blocker with SHT-1A autoreceptor antagonist properties, has in some studies increased symptomatology in some individuals with social phobia, although its effectiveness has not been demonstrated in randomized controlled trials.

**Monoamine Oxidase Inhibitors**

The MAOIs used to be the gold standard pharmacological treatment for social phobia, but they were eventually supplanted by the better tolerated and safer SSRIs and SNRIs. Phenelzine is the most widely studied MAOI, although tranylcypromine appears effective as well. Initial observations of their efficacy for the atypical subtype of depression characterized in part by marked sensitivity to rejection led to the use of MAOIs in social phobia, and they were subsequently demonstrated to be effective in randomized controlled trials. However, the use of MAOIs is associated with troubling side effects, including orthostatic hypotension, paresthesias, weight gain, and sexual dysfunction, as well as the need for careful attention to diet and use of concomitant medication because of the risk of potentially fatal hypertensive and serotonergic syndromes if the preparations are violated. As a result, these agents are generally reserved for use in patients failing to respond to easier-to-use agents.

**Benzodiazepines**

Although benzodiazepines have not been as well studied in SAD as in panic disorder, they appear to be effective, with available studies suggesting efficacy for agents such as clonazepam and alprazolam.
beginning as early as two weeks in non-depressed individuals. In addition to a relatively rapid onset of effect, they have a favorable side effect profile and efficacy on an as-needed basis for situational anxiety. Data from a randomized, double-blind, placebo-controlled study demonstrated that clonazepam augmentation of paroxetine was more effective than the SSRI alone in generalized SAD. Benzodiazepine administration may, however, be associated with treatment-emergent adverse effects including sedation, ataxia, and cognitive and psychomotor impairment, as well as the development of physiological dependence with regular use. Importantly, they are generally not effective against, and may in fact worsen, the depression that commonly presents comorbidly with social phobia. Individuals with a predisposition to or history of alcohol or substance abuse may be at risk to abuse benzodiazepines, and their potential negative interaction with concurrent alcohol use is a consideration given the elevated rates of alcohol and substance use among social phobics. Use of longer-acting benzodiazepines such as clonazepam is generally associated with less inter-dose rebound anxiety than occurs with shorter-acting agents and may therefore be useful for maintenance therapy, whereas a shorter-acting agent with a more rapid onset of effect such as alprazolam or lorazepam may reflect a more favorable profile for use on an as-needed basis for performance situations.

Other Agents

Tricyclic antidepressants (TCAs) do not appear to be effective for SAD, whereas small open trials suggest the potential efficacy of bupropion. The SHT-1A partial agonist buspirone has not demonstrated efficacy as a monotherapy for SAD, although one report suggests its potential utility as an adjunct for patients incompletely responsive to SSRI therapy. Small studies suggest the potential efficacy of atypical antipsychotics such as olanzapine, risperidone, aripiprazole, and quetiapine in SAD; however, given concerns about associated metabolic syndrome, weight gain, and extrapyramidal effects, their use is generally reserved for patients remaining symptomatic despite standard interventions.

Additionally, some anticonvulsants—including gabapentin, an alpha-2 delta calcium channel antagonist, and the related compound pregabalin—demonstrated efficacy for social phobia in randomized controlled trials. Valproic acid demonstrated suggestive evidence in an open trial in SAD, whereas results in small studies with levetiracetam have been mixed.

Discussion and Future Directions

A burgeoning of interest in the treatment of SAD has followed the growing understanding of the high prevalence, early onset, chronicity, morbid impact, and the associated family, social, and vocational function challenges to the field are to discover ways of optimizing use of the currently available agents and interventions and to develop novel therapeutics. An exciting development in translation research deriving from pre-clinical work on the neural circuitry underlying fear extinction led to the examination of D-cycloserine (DCS), a partial agonist of the N-methyl-D-aspartate (NMDA) receptor in the amygdala, as an agent capable of enhancing extinction learning, and was recently demonstrated to augment the response to CBT in individuals with social phobia. Replication and extension of this novel work holds the promise of improving outcomes for the treatment of SAD, as well as other fear-based disorders.